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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,867	BURNOUF ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-37* is/are pending in the application.

4a) Of the above claim(s) *27-32 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-26,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply, Sequence Alignment*.

DETAILED ACTION

Application Status

1. By virtue of a preliminary amendment filed on 12/21/2005, claims 1-19 have been canceled; and new claims 20-37 have been added. Thus, claims 20-37 are pending in this instant case.

Election

2. Applicant's election with traverse of Group I, (Claims 20-26 and 33-34) in the reply filed on 12/19/2007 is acknowledged. The traversal is on the ground(s) that the identified invention does not simply deal with a protein cyrstal including the processivity clamp factor of DNA polymerase and a peptide of about 3 to about 30 amino aicds, but with a crystal including a specific part of the processivity clamp factor of DNA polymerase. Applicants argue the disclosure of Kong et al. (which is recited in the search report of PCT/EP04/06942) is the admitance of consideration and/or search of all the claims of the present invention. Applicants also argue that the lack of unity during the international phase of the instant application was not raised. These are not found persuasive because of following reasons: (a) The crystal of Kong et al. disclose processivity factor which is encompassed by the instant technical feature of peptide comprising all or part of the processivity clamp factor binding sequence, wherein the part encompasses as small as any atom (e.g., water around or inside the crystal). Also. the crystal of Kong et al. comprise a peptide of about 3 to about 30 amino acids as shown in Figure 1 on page 426; (b) The teaching of Kong et al. was used to show that

the technical feature of invention (i.e., claimed protein crystal in claim 20 that can not encompass or represent the scope of all pending claims), which makes the instant technical feature does not constitute an advance over the prior art. (c) Finally, the fact that other examiner in the EPO did not raise the lack of unity before is not relevant to the lack of unity in the instant application. Group II-IV do not share the technical feature of Group I and do not relate to a single general inventive concept for the reasons stated previously and repeated above. Moreover, each Group represents a distinct independent invention and the search burden exists by virtue of the different class and subclass between the distinct inventions. Also, the search for each Group requires different key words because of the divergent subject matter. Searching together would create a serious search burden on the examination. The requirement is still deemed proper and is therefore made FINAL.

Claims 27-32 and 35-37 are withdrawn from consideration as non-elected inventions. Claims 20-26 and 33-34 will be examined herein.

Priority

3. The instant application is a 371 filing of the International Application No. PCT/EP04/06942, filed on 06/25/2004. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to a foreign patent application 03291596.9 (EPO, filed on 6/27/2003) in English.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed on 12/21/2005 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

(a) The structural coordinates in Figure 1 teach amino acid sequences since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

(b) The structural coordinates in page 5-8 in the specification teach amino acid sequences since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the specification.

(c) The polypeptide "RQLVGL" on the page 18, the last line, require appropriate SEQ ID NO.

(d) The structural coordinates in Claim 24 teach amino acid sequences since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the claim.

(e) Claim 24 recites many contiguous polypeptide within the coordinates. Any polypeptide having 4 or more amino acids should have SEQ ID NO.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or

1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

6. The specification is objected to because of the following informalities:

The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the name of the enzyme (β subunit of DNA Polymerase) and the source species (E. coli) for completeness.

Claim Objections

7. Claim 24 is objected to because of the following informalities:

(a) Claim 24 discloses many polypeptide sequences by the virtue of structure coordinates (as described above), which requrie a SEQ ID NO. Any polypeptide of 4 or more amino acid should have SEQ ID NOs. Appropriate correction is required.

(b) Claim 25 is objected to because of the use of abbreviation MES should be spelled out on first appearance in claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 20-26 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 20 recites "about 3 to about 30 amino acids, in particular of about 16 amino acids". The scope of intended range for a polypeptide length is unclear because it recites range within another range.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 20-24 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 is drawn to any protein crystal comprising the processivity clamp factor of DNA polymerase and a peptide of about 3 to about 30 amino acids, in particular of about 16 amino acids, said peptide comprising all or part of the processivity clamp factor binding sequence of a processivity clamp factor interacting protein, such as

prokaryotic Pol I, Pol II, Pol III, Pol IV, Pol V, MutS, ligase I, α subunit of DNA polymerase, UmuD or UmuD', or eukaryotic pol ε, pol δ, pol η,pol ι, pol κ. Claims 21-24 are protein crystal of Claim 20 with additional limitations recited in the claims.

While the structure and function of one species of said genera of IspA are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

Instant invention describes the co-crystal of *E. coli* β subunit of DNA polymerase III (encoded by the *dnaN* gene, without SEQ ID NO) in the presence of peptide of SEQ

ID NO: 1 as a binding ligand in the crystal, wherein the crystal consisting P1 triclinic space group, unit cell dimension of a=41.23, b=65.22, c=73.38, α=73.38 Å, β=85.58 Å γ=85.80 Å. While the claim language requires a function for the instant genera of crystals (that of the processivity clamp factor of DNA polymerase), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. The species noted above has adequately met this burden by the description in the instant specification. However, the composition of the crystals encompassed by the breadth of the claims is not described because the exact molecule is not limited nor the space group and unit cell dimensions associated with this breadth of chemical composition described. In Claims 23-24, only unit cell dimensions are adequately described. The exact polypeptide (SEQ ID NO is not disclosed in the instant application), even with a peptide ligand SEQ ID NO: 1 in Claims, accompanied by the word “comprising” does not disclose the exact composition of the protein crystal. The space group disclosed in Claims 22-24 satisfies one adequate description but missing the other two descriptions as noted above. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be

determined by analyzing that crystal's X-ray diffraction (Giege et al. Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the disclosed species of the instant disclosure. Therefore, claims drawn to the instant genera of crystals are also not adequately described.

10. Claims 25-26 are rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 25 is drawn to a method of obtain a protein crystal as defined in the Claim 20 comprising the following steps: (a) mixing a solution of processivity clamp factor of DNA polymerase, with a solution of a peptide of about 3 to about 30 amino acids, in particular of about 16 amino acids, said peptide comprising all or part of the processivity clamp factor binding sequence of a processivity clamp factor interacting protein, such as prokaryotic Pol I, Pol II, Pol III, Pol IV, Pol V, MutS, ligase I, α subunit of DNA polymerase, UmuD or UmuD', or eukaryotic pol ε, pol δ, pol η,pol ι, pol κ, and with a solution of MES pH 6.0 0.2 M, $CaCl_2$ 0.2 M, PEG 400 60%, to obtain a crystallisation drop, (b) letting the crystallisation drop concentrate against a solution of MES pH 6.0 0.1 M, $CaCl_2$ 0.I M, PEG 400 30%, by vapour diffusion, to obtain a protein crystal. Claim 26 is a method of Claim 25 with additional limitation as recited in the claim.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

Although, Example 1-1, on page 16, describes a method of crystallizing *E. coli* β subunit of DNA polymerase III (encoded by the *dnaN* gene, the exact protein sequence is not disclosed) wherein the crystal consisting P1 triclinic space group, unit cell dimension of a=41.23, b=65.22, c=73.38, α=73.38 Å, β=85.58 Å γ=85.80 in the presence of peptide of SEQ ID NO: 1 as a binding ligand in the crystal; the specification do not disclose a description of any protein crystallization that falls within the instant genera of crystallization that is a making crystal of any processivity clamp factor of DNA polymerase and any peptide as a ligand, wherein any peptide comprise all or part of the processivity clamp factor binding sequence of a processivity clamp factor interacting protein as recited in Claim 20, but not limited to recited proteins. A genus of proteins with a certain functional characteristic identity disclosed in Claims cannot be adequately described by the disclosure of the instant specification. The species of instant case does not correlate structure and function from species to genus. Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, a method of the crystallization encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification. In general, for a species of crystallization to be adequately structurally described, the following must be adequately disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations, pH and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (3) the

precipitant solution). The species of crystallization noted in Example 1-3 of the instant specification have adequately met this burden. However, the crystallization encompassed by the breadth of the claims is not described. A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al*. Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Therefore, the suitable condition disclosed in the specification (as shown in the Example 1-3 on page 16) cannot sufficiently describe a suitable condition of instant genus Claims comprising to crystallize very widely varying processivity clamp factor of DNA polymerase and any peptide of about 3 to about 30 amino acids as ligand. Thus, the instant specification and the prior art cannot describe the structure of a very broadly claimed genus method and one skilled in the art would not be in possession of the claimed genus by the instant specification.

11. Claims 20-26 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling a co-crystal and a method of making said co-crystal of *E. coli* β subunit of DNA polymerase III (encoded by the *dnaN* gene, without SEQ ID NO) in the presence of peptide SEQ ID NO: 1 (as a binding ligand in the crystal), wherein the crystal consists of a P1 triclinic space group, unit cell dimension of a=41.23, b=65.22, c=73.38, α=73.38 Å, β=85.58 Å γ=85.80 Å; does not reasonably provide enablement for all crystals and methods of preparation thereof as

broadly encompassed by the claims (i.e., any processivity clamp factor of DNA polymerase from any source with any peptide ligand having a certain length, wherein any peptide comprise all or part of the processivity clamp factor binding sequence of a processivity clamp factor interacting proteins including (but not limited) prokaryotic Pol I, Pol II, Pol III, Pol IV, Pol V, MutS, ligase I, α subunit of DNA polymerase, UmuD or UmuD', or eukaryotic pol ε, pol δ, pol η,pol ι, pol κ.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The breadth of the claims: Claims 20 and 25 (claims 21-24 and 26 dependent therefrom) is so broad as to encompass a protein crystal comprising any processivity clamp factor of DNA polymerase from any source with any peptide ligand having a certain length, wherein any peptide comprise all or part of the processivity clamp factor binding sequence of a processivity clamp factor interacting proteins including (but not limited) prokaryotic Pol I, Pol II, Pol III, Pol IV, Pol V, MutS, ligase I, α subunit of DNA polymerase, UmuD or UmuD', or eukaryotic pol ε, pol δ, pol η,pol ι, pol κ.

The nature of the invention: The invention is related to a co-crystal or a method of making said co-crystal of *E. coli* β subunit of DNA polymerase III (encoded by the *dnaN* gene, without SEQ ID NO) in the presence of peptide of SEQ ID NO: 1 as a binding ligand in the crystal, which results in a crystal with P1 triclinic space group, and unit cell dimension of a=41.23, b=65.22, c=73.38, α=73.38 Å, β=85.58 Å γ=85.80 Å. At the time of the invention, methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals, the state of the art at the time of

the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict a priori those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, Biophys Chem 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of

added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, e.g., pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Along these same lines, Wiencek (Ann Rev Biomed Eng, 1999, 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units…some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other processivity clamp factor of DNA polymerase and a peptide (as a ligand for co-crystal) described in Claim 20 and using the method described in Claim 25. Also, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of instant β subunit of DNA polymerase III of E. coli (as shown in Example 1, on page 16) can be achieved using any crystallization parameters encompassed in Claim 25.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of the claimed crystal and the method of crystallization thereof. See specification on page 16, Example 1-3. The prior art by Jeruzalmi et al. (2001, Cell, Volume 106, pages 417-428) teaches one species of crystal encompassed within the scope of instant Claims as described in 35 USC 102 below. Other than these two working examples, the specification fails to provide guidance for altering the crystallization conditions for crystallizing proteins comprising any processivity clamp factor of DNA polymerase from any source with any peptide ligand having a certain length, wherein any peptide comprise all or part of the

processivity clamp factor binding sequence of a processivity clamp factor interacting proteins including (but not limited) prokaryotic Pol I, Pol II, Pol III, Pol IV, Pol V, MutS, ligase I, α subunit of DNA polymerase, UmuD or UmuD', or eukaryotic pol ε, pol δ, pol η,pol ι, pol κ; with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a particular protein with or without ligands as evidenced by the above teachings. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to crystallization of other proteins can be crystallized under any different set of crystallization parameters encompassed by the term "comprising". In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is

unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Jeruzalmi et al. (2001, Cell, Volume 106, pages 417-428).

Claim 20 is drawn to any protein crystal comprising the processivity clamp factor of DNA polymerase and a peptide of about 3 to about 30 amino acids, in particular of about 16 amino acids, said peptide comprising all or part of the processivity clamp factor binding sequence of a processivity clamp factor interacting protein, such as prokaryotic Pol I, Pol II, Pol III, Pol IV, Pol V, MutS, ligase I, α subunit of DNA polymerase, UmuD or UmuD', or eukaryotic pol ε, pol δ, pol η,pol ι, pol κ.

Jeruzalmi et al. teach a protein crystal comprising "a truncated form of δ (δ^{1-140}, residues 1 to 140) makes contact with β" (see bottom middle of left column on page 418, and Experimental Procesures on page 426) and the structure is shown in Figure 2 on page 420. "The bacterial sliding clamp is composed of two β monomers arranged

head to tail in a circular dimer" (see right column, lines 11-12, on page 417); thus meets the limitation of "procesivity clamp factor of DNA polymerase" in Claim 20. Also the δ subunit having 140 amino acid meets the limitation of "about 16 amino acid" because the term "about" is not defined by the instant specification, it has been interpreted broad and reasonably to encompass 140 amino acid; thus, the δ subunit of Jeruzalmi et al. meets the limitation of "a peptide" comprising all or part of the pol δ in Claim 20. Thus, the protein crystal of δ: β complex as shown in Figure 2 meets all limitations of Claim 20.

13. Claims 33-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Dalrymple et al. (WO200238596, published 16-MAY-2002).

Claims 33-34 are drawn to a peptide of the SEQ ID NO: 1 or a pharmaceutical composition thereof.

Dalrymple et al. teach "peptides having eubacterial ß protein-binding properties and the surface of ß protein with which said peptides and other proteins interact. The invention provides in vitro and in vivo assays for identifying compounds that modulate the interaction between ß protein and proteins that interact therewith, and a method of controlling eubacterial infestation by modulating this interaction" (see Abstract)

Dalrymple et al. teach a peptide having 100% identity to SEQ ID NO: 1 in Example 1 of WO200238596 (see a peptide 138 on page 27, and Sequence Alignment in the attachment) which is capable of binding to a DNA polymerase β subunit for making antibacterial polypeptide. Dalrymple et al. also teach a tri-peptide QLD can be

synthesized, vacumm dried and dissolved in water in the Example 8 for testing antibacterial property; and the polypeptide 100% identical to SEQ ID NO: 1 by Dalrymple et al. would have made the same method with water, which meets the limitation of a pharmaceutically acceptable carrier. Thus, the peptide of Dalrymple et al meets the limitation of Claim 33-34.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652

Sequence Alignment
10561867

```
RESULT 1
ABG62310
ID   ABG62310 standard; peptide; 16 AA.
XX
AC   ABG62310;
XX
DT   15-JUN-2007  (revised)
DT   21-AUG-2002  (first entry)
XX
DE   Eubacterial DNA polymerase IV QLsLF motif containing peptide #40.
XX
KW   DNA polymerase III; beta subunit; eubacteria; antibacterial;
KW   eubacterial infection.
XX
OS   Escherichia coli.
XX
PN   WO200238596-A1.
XX
PD   16-MAY-2002.
XX
PF   08-NOV-2001; 2001WO-AU001436.
XX
PR   08-NOV-2000; 2000AU-00001320.
PR   06-FEB-2001; 2001AU-00002919.
XX
PA   (CSIR ) COMMONWEALTH SCI & IND RES ORG.
XX
PI   Dalrymple BP,  Kongsuwan K,  Wijffels GL,  Jennings PA,  Kemp GW;
XX
DR   WPI; 2002-471546/50.
DR   PC:NCBI; gi51247134.
DR   PC:BIND; 163504.
XX
PT   New molecule having surface analogous to surface of domain of eubacterial
PT   beta protein contacted by proteins that interact with beta protein,
PT   useful to identify inhibitors of beta protein-ligand interaction.
XX
PS   Example 1; Page 27; 326pp; English.
XX
CC   The invention relates to a molecule (I) comprising a surface (S)
CC   analogous to the surface of the domain of eubacterial beta protein
CC   contacted by proteins that interact with beta protein, where the surface
CC   is defined by the residues X(170), X(172), X(175), X(177), X(241),
CC   X(242), X(247), X(346), X(360), and X(362), where the superscript numbers
CC   designate the position of residues in Escherichia coli beta protein, or
CC   the equivalent residues in homologues from other species of eubacteria,
CC   and where: X(170) = Val, Ile, Ala, Thr, Ser or Glu; X(172) = Thr, Ser or
CC   Ile; X(175) = His, Tyr, Phe, Lys, Ile, Gln or Arg; X(177) = Leu, Met,
CC   Ile, Phe, Val or Ala; X(241) = Phe, Tyr or Leu; X(242) = Pro, Leu or Ile;
CC   X(247) = Val, Ile, Ala, Phe, Leu or Met; X(346) = Ser, Pro, Ala, Tyr or
CC   Lys; X(360) = Ile, Leu or Val; and X(362) = Met, Leu, Val, Ser, Thr or
CC   Arg. Also included are methods of identifying a modulator of the
CC   interaction between a eubacterial beta protein and proteins that interact
CC   with them, reducing (M4) the effect of eubacterial infestation of a
CC   biological system, involves delivering to a system infested with a
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CC   eubacterial species, a modulator of the interaction between eubacterial
CC   beta protein and proteins that interact with the beta protein; and (4) a
CC   template (II) for the design of a compound that binds to at least part of
CC   (S) of beta protein as defined above comprises a (P) such as X^1X^2,
CC   X^3X^1X^2, X^3X^1X^2X^4, GlnX^5X^3X^1X^2, GlnX^5XxX6X3X6, where: x = any
CC   amino acid residue; X^1 = Leu, Met, Ile, or Phe; X^2 = Leu, Ile, Val,
CC   Cys, Phe, Tyr, Trp, Pro, Asp, Ala or Gly; X^3 = Ala, Gly, Thr, Asn, Asp,
CC   Ser, or Pro; X^4 = Ala or Gly; X^5 = Leu; and X^6 = Leu, Ile, Val, Cys,
CC   Phe, Tyr, Trp or Pro. The method are useful for identifying a modulator
CC   of the interaction between a eubacterial beta protein and proteins that
CC   interact with the beta protein. (M4) is useful for reducing the effect of
CC   eubacterial infestation of a biological system. The compounds identified
CC   using above mentioned methods are useful as antibacterial agent for
CC   treatment or prevention of disease in humans, animals and plants. The
CC   present sequence is a eubacterial peptide from a DNA binding protein or
CC   polymerase which contains a DNA polymerase III beta subunit binding site
CC
CC   Revised record issued on 15-JUN-2007 : Enhanced with precomputed
CC   information from BOND.
XX
SQ   Sequence 16 AA;

  Query Match             100.0%;  Score 77;  DB 5;  Length 16;
  Best Local Similarity   100.0%;  Pred. No. 2.2e-06;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 VTLLDPQMERQLVLGL 16
              ||||||||||||||||
Db          1 VTLLDPQMERQLVLGL 16
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